BC Environment

A REVIEW OF THE ENVIRONMENTAL IMPACT AND TOXIC EFFECTS OF AZACONAZOLE

N.D. Henderson
Prepared for:
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SUMMARY

This paper summarizes the physical, chemical, environmental, and toxicological properties of the fungicide azaconazole, a chemical used in wood protection. It is active against several types of fungi, including basidiomycetes and ascomycetes, and fungi imperfecti.

Azaconazole undergoes photodegradation in water (half-life ~ one week), but is not expected to undergo hydrolysis. It is moderately to strongly adsorbed by soil depending on organic content, acidity, and temperature, and has a low leaching potential. Azaconazole undergoes biotransformation slowly (soil aerobic half-life of 355 days), and has a low potential to bioaccumulate.

Studies performed in rats showed that azaconazole is very rapidly absorbed, metabolised, and excreted in the urine and feces after oral administration. Some of the absorbed compound was observed in liver, kidney, and plasma at two hours post dose. The chemical was metabolised and excreted in the urine and feces, primarily as conjugated compounds.

According to toxicity scales used in this report, technical grade azaconazole is moderately to very toxic to experimental animals, depending on species tested and route of administration. The technical grade product is slightly toxic to fish, while one formulated product (Rodewod 200 EC) is considered moderately toxic to fish. Azaconazole is minimally to slightly irritating to skin, and non-irritating to severely irritating to eyes depending on purity and formulation. The compound may be a sensitizer, although it was considered a non-sensitizer in one maximization test. Tests performed *in vivo* and *in vitro* have produced acute reversible renal effects and altered organic ion transport in renal tissue. Carcinogenicity and several mutagenicity studies have all given negative results. There is no evidence of teratogenic potential, but maternal toxicity and fetotoxicity have been demonstrated.

Occupational exposure studies have not been done. However, related studies indicate that azaconazole levels in air should not pose health risks for persons in buildings containing azaconazole-treated wood. No significant dietary exposure to azaconazole is anticipated as a result of its use as an antisapstain.

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1.0 INTRODUCTION

Large volumes of chlorophenol compounds have previously been used in Canada to preserve and protect wood from attack by various pests. Concerns about acute aquatic toxicity, occupational impacts, and presence of hazardous impurities and breakdown products, including dioxins and furans, in chlorophenols are among the reasons for dissatisfaction with their use (1). The Canadian Lumber Industry has therefore phased out the use of chlorinated phenols for sapstain control, and the use of alternative chemicals has increased. Currently, several pesticides which are fully or temporarily registered by Agriculture Canada may be used for the protection of freshly cut lumber. These antisapstain materials may contain one or more of the following "active" ingredients: 2-(thiocyanomethylthio)benzothiazole (TCMTB), 3-iodo-2-propynyl butyl carbamate (IPBC), didecyldimethylammonium chloride (DDAC), sodium carbonate, sodium borate, azaconazole, and copper-8-quinolinolate (Cu-8).

The purpose of this paper is to review and evaluate the available information concerning the physical and chemical properties, environmental effects, and toxicity of azaconazole. Studies supplied by the manufacturer, Janssen Pharmaceutica of Titusville, NJ, form the basis for this report. Additionally, computerized data bases, listed in Appendix A, also provided some information on the chemical.

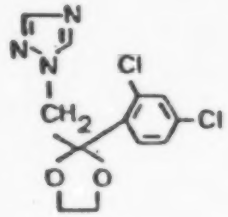
2.0 HISTORICAL BACKGROUND AND USES

Azaconazole was granted full registration for formulating non-food use pesticides on September 26, 1990 (3). In Canada, azaconazole is marketed for antisapstain use as an emulsifiable concentrate (EC), under the name Rodewod 200EC (4). This formulation contains a minimum of 18% azaconazole (4), and is active against basidiomycete and ascomycete fungi, and fungi imperfecti (5). It was granted temporary registration for use in sapstain control on September 27, 1990.

Azaconazole can be used in water-based formulations which include emulsifiable concentrates (EC), flowables, and soluble liquids (SL) (7). It may be used for protection of wood and wood-modified products (6).

3.0 PHYSICAL AND CHEMICAL PROPERTIES

The generic (IUPAC) name for azaconazole is 1-[∝[2-(2,4-dichlorophenyl)-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole. Its structure is shown below.



(CAS No. 60207-31-0)

The technical product is a beige to brown coloured powder, minimum 90% pure. It has a slight phenol-like odour, a boiling point of 450°C, a melting range of 104-112°C (7), a measured melting point of 112.1°C (29), and a specific gravity of 1.46 g/ml (6). The vapour pressure is 8.6 x 10^{-5} Pa at 20°C (7). At higher temperatures, vapour pressure ranges from 6.14 Pa (133.3°C) to 40.6 Pa (163.7°C) (29). It is 0.3% volatile by weight (24 hours at 100°C) (7).

Azaconazole is stable when stored at room temperature and protected from light; shelf life is reportedly more than 5 years (7). It is qualitatively stable up to 95°C for 8 hours, and is stable up to approximately 220°C (5). It is stable in acid and alkaline solutions (pH 1 to 9) when stored at temperatures up to 40°C (5). However, contact with strong acids and oxidants is to be avoided (6), as is contact with acetone or cyclohexanone to avoid photodegradation.

Azaconazole is insoluble in water (~0.3 g/L) (30), slightly soluble in 2-propanol, xylene, and ethylene glycol, moderately soluble in n-butanol, MIK, and propylene glycol, and soluble in chloroform, acetone, benzene, and toluene (6). Log n-octanol/water partition coefficients (log Kow's) of 2.17 (4, 31) and 2.36 (6) have been reported.

Combustion of azaconazole is reported to produce nitrous oxides and hydrogen chloride, though combustion conditions were unspecified (6). A report from the manufacturer on the combustion of radiolabelled azaconazole between 250° and 490°C (32) stated that azaconazole was not transformed at temperatures up to 440°C. Above 440°C, a small amount of a tentatively identified ketone (∝-(2,4-dichlorophenyl)-1H-1,2,4-triazole 1-ethanone), originating from scission of the dioxolane ring, was produced. At 490°C, radiolabelled azaconazole self-ignited and several transformation products, including $^{14}CO_2$ and the previously mentioned ketone, were observed. Further characterization of products was not feasible, as none were produced in significant amounts (32).

4.0 ENVIRONMENTAL IMPACT

4.1 Environmental Sources

Azaconazole is not likely a naturally occurring substance. Sources in the environment could include spills, permitted and unpermitted discharges from commercial facilities using the chemical, and discharges from products treated with azaconazole, including wood and wood products.

4.2 Environmental Distribution

No studies measuring azaconazole levels in water or soil were located. Section 4.3.8 summarizes work done on azaconazole levels in air.

4.3 Environmental Behaviour

Several studies on various aspects of environmental fate have been submitted by the manufacturer (33-42). These are summarized below.

4.3.1 Hydrolysis

One study on the hydrolysis of azaconazole under simulated natural conditions was obtained from the manufacturer (33). Aqueous ^{14}C-azaconazole solutions of 20 ug/mL (ppm) were incubated for 62 days at pH's of 5.0, 7.0, and 9.0 in the dark at 25°C under sterile conditions (33). Analysis showed that azaconazole was not degraded under these conditions. Chemical hydrolysis is therefore considered to be an unlikely dissipation mechanism for azaconazole in the aquatic environment.

4.3.2 Phototransformation

One study on the phototransformation of azaconazole in a simulated aquatic environment involved artificial sunlight irradiation of 10 ug/mL solutions of radiolabelled azaconazole in buffer at pH 7; in buffer (pH 7) : acetone (98:2); or in membrane sterilized surface water (34). The buffer and surface water solutions were irradiated for 1, 2, 3, 4, 7, 10, and 14 days, while the acetone-sensitized solution was irradiated for 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 168 hours. The half-life of azaconazole was 3.5 days in the buffer solution, and 7.8 days in the surface water (34). In buffer with 2% acetone, the half-life was 4.0 hours. Reverse-phase high performance liquid chromatography (HPLC) indicated that the parent compound was progressively transformed into very polar products, probably containing remnants of the phenyl ring. The latter products were ultimately mineralized. Radioactivity in the form of $^{14}CO_2$ was also detected. In the acetone solutions, photoproducts of intermediate polarity were isolated and analyzed. A triazolodihydroisoquinoline ring system was formed by cyclization between the triazole ring and the chlorophenyl ring.

4.3.3 Soil Adsorption/Desorption

Two studies on soil adsorption/desorption of azaconazole were supplied by the manufacturer. When tested in eight soil types, azaconazole was moderately strongly to strongly adsorbed (8, 35). Soils tested included acidic sand and sandy loam at pH 4-5, and a silty loam at pH 7.5. Soil organic content ranged from 1.13% to 8.63% (8). Results showed that adsorption increased with organic matter content, soil acidity, and decreasing temperature.

In the second study (36), sorption on soil was investigated at room temperature on two silt loams, a sandy loam, and a sand. Adsorption coefficients ranged from 2.13 for the low organic matter sand to 8.18 for the high organic matter sandy loam. Sorption on these soils was reversible to a large extent; desorption was inversely related to adsorption intensity and to initial sorbate loading (36).

4.3.4 Leaching

A study on the mobility of azaconazole in soils found that the compound had a low leaching potential (37). Approximately 30 cm of water was leached at room temperature through 40 cm of segmented columns over 3 days. The columns were packed with six different soil types and loaded with 0.2 mg of ^{14}C-labelled azaconazole. No radioactivity above blank level was detected in the leachates. In a soil with low retention capacity, the maximum concentration of azaconazole occurred in the 7.5-10 cm segment, with an average migration depth of 7.5 cm and no leaching beyond 15 cm. In a soil with high retention capacity, maximum azaconazole concentration occurred in the 0-2.5 cm segment, while the average leaching depth was 2.4 cm. No migration was detected beyond 7.5 cm. It was estimated that on average, an annual drainage of 30 cm will transfer azaconazole 4.8 cm in the soil profile (37).

4.3.5 Aerobic Soil Metabolism

An aerobic soil metabolism study involved treatment of a continuously aerated silt loam with 1 mg of ^{14}C-azaconazole per kg soil and incubation at room temperature for 300 days (38). The half-life of azaconazole was calculated to be 355 days. At the end of the incubation period, 13.5% of the applied concentration had been transformed into "soil-bound" residue; a further 29% was mineralized and ultimately evolved as $^{14}CO_2$. No major biotransformation products intermediate between azaconazole and carbon dioxide were detected (38).

4.3.6 Anaerobic Soil Metabolism

An anaerobic soil metabolism study supplied by the manufacturer involved incubating an anaerobic sandy loam at 25°C with ^{14}C-azaconazole at a level of 5 ug/g soil (39). Soil samples were analysed immediately after treatment, and after 0.5, 1, and 2 months. All extractable radioactivity was accounted for by the parent

compound, accounting for 77.5% of the administered amount after 2 months. The projected first-order half-life was 5.8 months. Approximately 10% of the original concentration was converted to "soil-bound" residues during the 2-month incubation period (39).

4.3.7 Aerobic Aquatic Metabolism

To follow the aquatic fate of ^{14}C-azaconazole, mixed-phase flow-through metabolic systems containing either soil/water, sediment/brookwater, or activated sludge were incubated at 20°C with continuous aeration over 60 days (40). ^{14}C-Azaconazole was added to each system at a concentration of 5 mg/L. A material balance for azaconazole-derived radioactivity in solution, solid, and gas phases was produced.

The half-life of azaconazole was 66 days in the soil/water system, and 141 days in the sediment/brookwater system. The half-life in the sludge system was 190 days, although sludge apparently was not suitable as an inoculum for transformation studies of the kind described (40).

In the soil/water and sediment/brookwater systems, the azaconazole-derived material distributed to the solid phase due to the formation of unextracted residues. One transformation product, α-(2,4-dichlorophenyl)-1H-1,2,4-triazole-1-ethanol, resulting from dioxolane scission, was isolated. The ultimate degradability of azaconazole in aerobic aquatic environments was demonstrated by the formation of very polar transformation products and carbon dioxide (40).

4.3.8 Volatilization

Two studies on volatilization from wood and aerial levels of azaconazole reported low aerial concentrations in areas exposed to treated wood (41, 42). In the first study (41), pine sapwood blocks were vacuum-impregnated with two types of formulations containing radiolabelled azaconazole: an oil miscible liquid (OL) and a water soluble liquid (SL). Active ingredient retentions of 0.857 kg/m^3 and 1.043 kg/m^3 were reported for the OL and the SL, respectively. Treated blocks were end-sealed then exposed to aeration at 100 L/h for 74 days. After passing over the blocks, air was analysed for azaconazole by radio-counting (Detection Limit, DL of 100 ng azaconazole-equivalents per mL) and by gas-liquid chromatography with electron capture detection (GLC-ECD) (DL of 5 ng/mL).

Results showed identical volatilization patterns for both treatments. Azaconazole was not detected for days 0 to 25, or for days 53 to 74 when GLC-ECD analysis was used. From 26 to 52 days, azaconazole was detected in aerial samples: levels were less than 1 ug/m^2/hr, corresponding to aerial levels of less than 0.5 ug/m^3. Differences in volatility rates over time were not accounted for in the report. It was concluded that the use of azaconazole in wood preservation will not induce hazardous aerial levels in areas exposed to treated wood (41).

The second study (42) involved experimental remedial treatment of roof-timbers with a formulation containing 5.2 g azaconazole/L, at an application rate of 450 mL remedial fluid per m^2 of wood. Air samples were collected from the loft space ten days after treatment, using liquid impingers (methanol; 2-propyl alcohol) and solid absorbents (Amberlite XAD-2) as absorber traps. Analysis was by GLC-ECD with a sensitivity of 0.1 ng/mL (DL in sampled air = 25 ng/m^3).

Ten days after treatment, the maximum concentration recorded in the roof void was 0.6 ug/m^3. The study concluded that based on animal toxicity data, such low levels are not expected to incur health risks for occupants of treated buildings (42).

An addendum to the second study (42) reported the results of air samples collected in the living room and loft space of the house treated previously. At three and six months after treatment, aerial levels were less than 0.1 ug/m^3 at each sampling time.

5.0 PHARMACOKINETICS

5.1 Absorption, Distribution, Metabolism, and Excretion

Three excretion/metabolism studies using fasted rats were available from the manufacturer (78-80). In the first study (78), male and female Wistar rats were dosed orally with 0.5 or 5.0 mg ^{14}C-azaconazole/kg body weight. The compound was rapidly and completely absorbed, and thoroughly metabolised with substantive biliary metabolic excretion. Total radioactivity levels disappeared from the body with an apparent elimination half-life of 7.7 hours. In the 5 mg/kg group, radioactivity levels two hours after dosing were highest in the liver (5.3 ug/g, 3.2% of administered radioactivity) and kidney (2.3 ug/g). Radioactivity in the stomach (2.1% of dose) was exclusively due to the parent compound, although only half of the radioactivity in the liver could be attributed to the parent compound. At 8 hours post-dose, a peak plasma concentration of 0.34 ug/mL was recorded, and levels of 0.1 to 0.3 ug/g were recorded in all other tissues. At 24 hours post-dose, levels in the brain and fat were virtually undetectable; at 96 hours, radioactivity could be detected only in the liver, kidney, and lung. Only negligible amounts of radioactivity (<0.5% of parent dose) persisted in all other tissues 96 hours after drug administration. Maximum cumulative amounts of 42% and 39% of total administered radioactivity were excreted within 24 hours, as metabolites in the urine and feces, respectively (78).

In the second study, four male Wistar rats were administered ^{14}C-azaconazole at 5 mg/kg (79). Results indicate that azaconazole was well absorbed and extensively metabolised. Urinary and fecal excretion of the administered radioactivity was very rapid and complete, with 89.4% and 94.1% excreted at 24 and 96 hours post-dose, respectively. Azaconazole was not detected in urine or feces upon analysis, although nine metabolites were purified from urine and

characterized by HPLC co-chromatography and/or MS. Two main metabolites in the urine and feces each accounted for about 17% of the dose. In the urine, these two metabolites were present mainly as conjugates. An extensive metabolic scheme, involving several metabolic pathways, was deduced. The nine identified metabolites resulted from scission of the dioxolane ring, with subsequent reduction of the resulting ketone (79).

The third pharmacokinetic study in rats involved dosing male and female rats orally with ^{14}C-azaconazole at 5 and 0.5 mg/kg, and dermally with 5 mg ^{14}C-azaconazole/kg (80). Excretion was again rapid and complete in all groups dosed orally, although small differences were observed between groups. At both doses, ^{14}C clearance in females was more rapid and abundant in the urine but slower and less abundant in the feces than was observed for males. Dermal application resulted in very low absorption and excretion, with only 1% of the applied dose excreted in urine and feces after 24 hours, and 3% excreted after 48 hours.

Orally administered azaconazole was extensively metabolised in all groups, metabolite mass balance in urine and feces being similar for all dose groups. The parent compound was not detected in any metabolised samples (80).

In a separate study, beagle dogs administered oral dosages of 2.5, 10, or 40 mg/kg azaconazole as either a single dose or as daily doses over six months showed similar plasma levels between groups for comparable dose intervals (81). This demonstrated that the bioavailability was not altered during the course of the experiment. Daily doses of 2.5 mg/kg were almost completely eliminated by first-pass metabolism, but higher dose levels resulted in peak levels increasing exponentially with increasing dose. Saturation of the hepatic metabolising enzymes was therefore suggested. Liver enzyme induction or inhibition apparently did not occur. Plasma levels decreased with a terminal half-life of between 1.1 and 2.4 hours, independent of dose regimen. There was no evidence of bioaccumulation in the tissues after repeated dosing (81).

5.2 Placental and Milk Transfer

No placental or milk transfer studies were available for review.

6.0 TOXICOLOGICAL EFFECTS

6.1 Mammalian Toxicity

Several mammalian toxicity test results are presented below. The formulations and species tested, and the toxicity values reported in the original source, are listed here. As well, a value converted to show toxicity based on **100% active ingredient** (i.e. 100% azaconazole) is listed in the "Converted" column. The converted toxicity value was obtained by multiplying the toxic dose of the formulation by the percent content of azaconazole in the formulation. Toxicity

ratings, based on the converted value, follow each acute oral, dermal, and inhalation toxicity value and reference, according to the table in Appendix B. Rodewod refers to the Rodewod 200 EC emulsion concentrate, a formulation containing minimum 18% azaconazole.

a) Acute Oral LD50:

Formulation	Species	Reported LD50	Converted (100% AI)	Toxicity
85% azaconazole	Rat	308 mg/kg (4,51)	262 mg/kg	4
Rodewod	(males)	1901 mg/kg (61)	342 mg/kg	4
Rodewod	(females)	923 mg/kg (61)	166 mg/kg	4
Rodewod	(combined sexes)	1291 mg/kg (4, 61)	232 mg/kg	4
96.9% azaconazole	Rabbit	324 mg/kg (4, 53)	314 mg/kg	4
~100% azaconazole	Mouse	1123 mg/kg (7, 52)	1123 mg/kg	3
Rodewod	Dog (males)	1570 mg/kg (62)	283 mg/kg	4
Rodewod	(females)	1240 mg/kg (62)	223 mg/kg	4
Rodewod	(combined sexes)	1390 mg/kg (4, 62)	250 mg/kg	4

b) Acute Dermal LD50:

Formulation	Species	Reported LD50	Converted (100% AI)	Toxicity
~100% azaconazole	Rat	>3100 mg/kg (4, 54)	>3100 mg/kg	3
85% azaconazole	Rat	>2560 mg/kg (7)	>2176 mg/kg	3
Rodewod	Rabbit	>2000 mg/kg (63,86)	>360 mg/kg	4
95.5% azaconazole	Rabbit	>2000 mg/kg (55)	>1910 mg/kg	3

c) Primary Eye Irritation:

Formulation	Species	Reported Effect
20% azaconazole (0.1 mL)*	Rabbit	non-irritating (4, 57)
85% azaconazole (0.1 g)	Rabbit	mildly irritating (6, 58)
Rodewod (0.1 mL)	Rabbit	moderately to severely irritating** (4, 65)

* Repeated daily dosage over four weeks
** Irreversible corneal damage also reported

d) Primary Skin Irritation:

Formulation	Species	Reported Effect
96.9% azaconazole	Rabbit	mildly irritating (4, 59)
Rodewod	Rabbit	slightly irritating (4, 66)
95.5% azaconazole	Rabbit	non-irritating (55)

e) Dermal Sensitization:

Formulation	Species	Reported Effect
93.7% azaconazole	Guinea Pigs	non-sensitizing (4,60)
96.9% azaconazole	Guinea Pigs	weakly sensitizing (4)
Rodewod	Guinea Pigs	non-sensitizing (4)
Rodewod	Guinea Pigs	weakly sensitizing (67)

f) Acute Four Hour Inhalation LC50:

Formulation	Species	Reported LC50	Converted(100% AI)	Toxicity
~100% azaconazole	Rats	>0.04 mg/L (56)	>0.04 mg/L	5*
~100% azaconazole	Rats	>0.064 mg/L (56)	>0.064 mg/L	5*
Rodewod	Rats	1.48 mg/L (4)	0.266 mg/L	4
Rodewod	Rats	1.22 mg/L (64)	0.22 mg/L	4
Rodewod	(males)	1.06 mg/L (64)	0.19 mg/L	5
Rodewod	(females)	1.42 mg/L (64)	0.26 mg/L	4

*Toxicity ratings may be lower (LC50 values higher) since the tested concentrations are the maximum attainable for the particle size (14).

g) Intraperitoneal Toxic Effects

The effects of azaconazole on kidney function have been studied in rats (10). Male F344 rats were given either a single intraperitoneal injection of 0.4, 0.6, or 1.0 mmol azaconazole/kg (120, 180, or 300 mg/kg), or seven daily doses of 0.1 or 0.3 mmol azaconazole/kg (30 or 90 mg/kg). The animals were observed for clinical signs of toxicity, and food and water intakes were monitored. Urine samples were collected at selected times for determining standard renal function parameters, and blood samples were analyzed for blood urea nitrogen (BUN). The animals were killed 48 hours after the last injections, and the kidneys were removed, weighed, and examined for histopathological changes.

Animals in all dose groups exhibited decreased food and water intakes. All animals receiving the 1.0 mmol/kg dose died within 30 hours, and were anuric. No deaths occurred among the other treated animals, although the 0.4 and 0.6 mmol/kg doses significantly decreased urine volume at six hours post-dose. Urine volume in the 0.4 mmol/kg group returned to normal after 48 hours, but the volume in the 0.6 mmol/kg group did not. Proteinuria and slight hematuria were observed in the 0.6 mmol/kg group. Accumulation of p-aminohippurate (PAH), but not tetraethylammonium ion (TEA), was stimulated by the 0.4 and 0.6 mmol/kg doses. Neither dose affected BUN concentration or kidney weight, and no treatment-related histopathological changes were observed. Daily administration of 0.1 or 0.3 mmol azaconazole/kg did not significantly affect any of the parameters studied. The authors concluded that azaconazole produces acute, reversible renal effects at doses of 0.6 mmol/kg or less, and alters organic ion transport *in vivo* (10).

h) *In vitro* Studies

In vitro effects of azaconazole on the accumulation of organic ions were examined in one study (10). Renal cortical slices were incubated with 0.01 to 1.0 mmol azaconazole, and the effects of basal and lactate stimulated PAH and TEA uptake by the slices were evaluated. All concentrations of azaconazole significantly decreased TEA uptake. The 0.01 and 1.0 mmol doses decreased PAH uptake, but 0.1 mmol azaconazole stimulated PAH uptake. It was concluded that azaconazole can alter organic ion transport *in vitro*.

i) Feeding Studies:

Several mammalian feeding studies are available, and are summarized below. A 90-day feeding study on rats and dogs gave no observed effect levels (NOELs) of 200 mg/kg of food and 10 mg/kg body weight/day, respectively (7). Further details of the study were not provided.

In a 6-month dog study, 3 animals of each sex received 2.5, 10, or 40 mg azaconazole/kg/day orally via gelatin capsules (82). There were no effects on behaviour, hematological parameters, urinalysis, and gross pathology. At 10 mg/kg, an increase in alkaline phosphatase levels was observed. At 40 mg/kg, decreases in body weight gain and food consumption, and increases in alkaline phosphatase and relative weights of several organs (lungs, spleen, liver, heart, kidneys, brain, thyroids, and hypophysis) were observed. The increase in organ weights was also correlated with a lower body weight gain. The NOEL was established at 10 mg/kg/day based on these studies (82).

A 24-month combined chronic toxicity and carcinogenicity study in Wistar rats was conducted with dose levels of 0, 50, 200, and 800 ppm of 93.1% pure azaconazole (83). These dose levels approximately correspond to 3.08, 12.5, and 51.2 mg/kg in males, and 4.35, 18.2, and 70 mg/kg in females. No drug-related mortality was observed at any dose. At 800 ppm, decreased weight gain and food consumption, hematological and clinical chemistry changes, and histological liver changes were observed. There were no observable effects on organ weights, gross pathology, and urinalysis parameters. There was no evidence for carcinogenic potential. The NOEL for chronic toxicity was determined to be 200 ppm (12.5-18.2 mg/kg).

A 20-month carcinogenicity study in mice (84) found a minimally toxic dose of 40 mg azaconazole/100 g food (~80 mg/kg body weight), as evidenced by a slight decrease in body weight gain in both sexes. In females dosed with 2.5 and 40 mg/100 g food (5 and 80 mg/kg body weight), a statistically increased incidence ($p<0.05$) of non-tumourous lung tissue mass was noted (84). There was no evidence of carcinogenic potential (4).

6.2 Fish Toxicity

Toxicity values for several species of fish are presented below. Values are for either 100% active ingredient (i.e., azaconazole), a nominal value of 100% active ingredient, or a reported concentration (i.e., 95.2% azaconazole for zebra fish). For comparative purposes, data on the toxicity of the Rodewod formulation are also listed, and converted to show toxicity based on 100% azaconazole. This conversion shows that the toxicity of the formulation is greater than the toxicity of technical grade azaconazole. Toxicity ratings follow each toxicity value and reference listed below, according to the table in Appendix C.

96 hr LC50:

Concentration	Species	96 hr LC50	Toxicity
100% azaconazole	Rainbow Trout	24 mg/L (4, 45)	2
100% azaconazole	Rainbow Trout	20.8 mg/L (45)	2
100% azaconazole	Chinook Salmon	26.9 mg/L (4, 45)	2
Nominal 100%	Brown Trout	22 mg/L (4, 44)	2
Nominal 100%	Bluegill Sunfish (14°C)	14 mg/L (4, 44)	2
Nominal 100%	Bluegill Sunfish (20°C)	32 mg/L (4)	2
Nominal 100%	Carp	17 mg/L (4, 44)	2
Nominal 100%	Catfish	37 mg/L (4, 44)	2
Nominal 100%	Golden Orfe	30 mg/L (4, 44)	2
95.2% azaconazole	Zebra fish	36.9 mg/L (47)	2
100% azaconazole*	Zebra fish	35.1 mg/L (47)	2

* converted from 95.2% azaconazole toxicity value for zebra fish by multiplying 36.9 mg/L by 0.952

Formulation (96hr)	Species	Reported LC50	Converted (100%AI)	Toxicity
Rodewod	Rainbow Trout	14.6 mg/L (85)	2.9 mg/L (85)	3
Rodewod	Chinook Salmon	11.3 mg/L (85)	2.3 mg/L (85)	3

4-day LC50: Bluegill Sunfish (pH 8.2) 18 to 32 mg/L (43)

28-day Toxicity

The prolonged toxicity of azaconazole to zebra fish was investigated in a semi-static fish test over 28 days (49). The No Observed Effect Concentration (NOEC) with respect to mortality was >18 mg azaconazole per litre. The NOEC with respect to behaviour was 5.6 mg/L. The NOEC for reversible adverse effects, including reduced food intake, slowed movement, hyperventilation, and loss of equilibrium, was 18 mg/L (49).

6.2.1 Bioaccumulation

The bioaccumulation potential of azaconazole was investigated in zebra fish using an eight-day static exposure test at concentrations of 0.5 and 0.05 mg azaconazole/L (50). Bioconcentration factors (BCFs) of 1.27 and 1.81 were calculated for the 0.5 mg/L and 0.05 mg/L concentrations, respectively. These

BCFs are markedly lower than theoretical predictions based upon the Kow and aqueous solubility of azaconazole (BCF ~ 4.33 to 4.40). It was concluded that fish were probably transforming the test substance, which prevented a build-up in their tissues (50).

6.3 Zooplankton Toxicity

			Toxicity
48 hr LC50:	*Daphnia magna*	86 mg/L (43)	
96 hr LC50:	Mysid shrimp	27.7 mg/L (46)	2

6.4 Algal Toxicity

7-Day Growth EC50:	*Selenastrum capricornutum*	32-100 mg/L

6.5 Avian Toxicity

Acute Oral LD50:	Japanese Quail	~500 mg/kg (6)
Dietary LC50	Japanese Quail	>1000 ppm (6)
	Mallard Duck	>5000 ppm (6)
	Ring-Necked Pheasant	>5000 ppm (6)

6.6 Comparative Toxicity

Oral, dermal, and aquatic toxicity values for several antisapstain compounds are listed in Table 1. Comparatively, azaconazole is one of the more orally toxic but one of the least aquatically toxic antisapstain active chemicals available in Canada. However, the formulated product, Rodewod 200 EC, shows increased toxicity to fish over that of the active ingredient. Since the aquatic environment may potentially receive a large portion of runoff from lumber yards using antisapstain chemicals, a relatively low aquatic toxicity is important for the protection of aquatic species.

7.0 CARCINOGENICITY

Two carcinogenicity studies supplied by the manufacturer show negative results for the species tested (83, 84). In the first study, male and female Wistar rats received dietary doses of 50, 200, or 800 ppm azaconazole per day for 24 months (83). These doses corresponded to approximately 3.08, 12.5, and 51.2 mg/kg in males, and 4.35, 18.2, and 70 mg/kg in females. Although chronic toxicity effects were noted (see section 6.1), azaconazole did not produce any carcinogenic effects (83).

In the second study, albino Swiss mice were dosed with 2.5, 10, and 40 mg azaconazole/100 g of food for 22 months (84). These doses corresponded to

approximately 5, 20, and 80 mg/kg body weight. No evidence of carcinogenic activity was noted at these doses (84).

8.0 MUTAGENICITY

Several mutagenicity studies conducted with azaconazole have all produced negative results (4, 68-74). Tests using highly purified azaconazole (99.1-99.2%) included the Ames assay, the mouse micronucleus test, and the dominant lethal assay in male mice (4).

8.1 Gene Mutation

In an Ames reversion mutation assay using *Escherichia coli* strain WP2 uvrA- (68), dose levels up to 5000 ug/plate were tested. Results were negative in both the presence and absence of rat liver metabolic activation. A second Ames assay (69) using the five standard *Salmonella typhimurium* strains (TA1535, TA1538, TA97, TA98, and TA100) in the presence and absence of metabolic activation at dosages of 250 to 5000 mg azaconazole per plate showed no indication of mutagenic activity.

A sex linked recessive lethal test in *Drosophila melanogaster* (70) involved dosing Berlin K males with 100 and 400 ppm azaconazole for three consecutive days. Results were negative for genotoxic mutation in all stages of the male germ cells.

8.2 Structural Chromosome Aberration

The induction of structural and numerical chromosome aberrations in bone marrow cells of mice was assayed after single oral administration of 40, 160, or 640 mg azaconazole/kg (71). A total of 1000 polychromatic erythrocytes (PCEs) per animal were screened for the presence of micronuclei. Dose levels in the absence of rat liver S-9 were 33.3, 60, and 100 ug/mL of culture. In the presence of S-9, levels were 100, 333, and 600 ug/mL. Results were negative for an increase in PCEs, indicating that azaconazole has no chromosome-damaging nor spindle-poisoning potential to PCEs of mice (71).

The effect of azaconazole on the induction of chromosome aberrations in cultured peripheral human lymphocytes in the presence and absence of a metabolic activation system was also evaluated (72). Results indicate that azaconazole is not clastogenic in human lymphocytes, either in the presence or absence of a metabolic activation system.

8.3 DNA Repair

The effect of azaconazole on DNA repair, measured as unscheduled DNA synthesis (UDS) in a primary rat hepatocyte culture, gave negative results for the concentrations tested (0, 7.5, 20, 75, 100, 150, and 200 ug/mL of culture) (73).

8.4 Other Tests

An SOS chromotest using *E. coli* was conducted with azaconazole in the presence and absence of a rat metabolic activation system (74). In this test an unrelated enzyme gene for ß-galactosidase, normally absent from *E. coli,* was linked to an SOS operator gene. When the SOS system is activated by genotoxic assault, the enzyme is produced and can be easily detected (74).

No increase in ß-galactosidase activity was detected at azaconazole concentrations up to 10,000 ng/well, with or without metabolic activation. The results imply that azaconazole has no genotoxic potential towards *E. coli* under these test conditions (74).

9.0 TERATOGENICITY AND REPRODUCTIVE EFFECTS

Several teratogenicity and reproduction-related studies have been supplied to the federal (4) and/or BC provincial governments (76-77). However, only two are summarized below; others submitted to the federal government (4) have been judged unacceptable, and therefore are not reported below.

A teratogenicity study using rats dosed orally with 93.4% azaconazole found a NOEL of 40 mg/kg/day for maternal toxicity and fetotoxicity (4). There was no evidence of teratogenicity at the highest dose tested, 60 mg/kg (4, 76).

A teratogenicity study in rabbits (77) dosed orally with 94.5% azaconazole produced evidence of maternal toxicity at 160 mg/kg/day, with mortality, clinical signs, and premature deliveries observed. Maternal toxicity was not evident at 40 mg/kg/day. In terms of fetotoxicity, a NOEL of 160 mg/kg/day was established. Teratogenic effects were also not evident at this dose. The NOEL for maternal toxicity in rabbits was set at 80 mg/kg/day by the federal government (4).

10.0 OCCUPATIONAL EXPOSURE

Three studies related to occupational exposure effects have been submitted by the manufacturer in support of azaconazole registration (4). In a laboratory study, pine sapwood was dip-treated with azaconazole and levels in air were monitored as the chemical volatilized from the wood (11, 41, 42). A model for the calculation of volatilization rates and aerial concentrations of azaconazole was described. The authors concluded that azaconazole has a very low volatilization

rate from treated pine sapwood and that aerial levels do not pose a health risk to persons in treated buildings. These conclusions were based on extrapolation from animal toxicity data.

The other two studies (4) involved direct measurement of airborne azaconazole in two rooms of a house after injection and spray treatments of the roof beams. The air concentrations in these studies were used to estimate incidental respiratory exposure in treated rooms. Quantification of air levels after the specific treatment scenarios resulted in a low exposure estimate (see Section 4.3.8).

The utility of the conclusions from these studies for risk assessment is limited since they involved air monitoring only, and did not address dermal exposure, exposure during application of the chemical, or provide data relating to potential respiratory exposure (4). Since wood treatment presents a significant potential for both dermal and inhalation exposure, estimates of such exposure potentials are essential for occupational risk assessment.

11.0 FOOD EXPOSURE

The manufacturer apparently intends to pursue registration of azaconazole for food contact use, although no supporting data required for such registration have been submitted to government regulators (4). Since relevant data are not available, an evaluation of the health and safety of dietary exposure to azaconazole residues is not possible at this time.

The proposed label for azaconazole states that treated sawdust or other wood wastes should not come in contact with domestic animals, or be used as a mulch for living plants (4). The federal government of Canada has further recommended against using azaconazole treated wood for the construction of food holding containers, food storage facilities, or food growing buildings (4). In view of these prohibitions, no significant dietary exposure to azaconazole is anticipated as a result of the proposed antisapstain use (4).

12.0 ANALYTICAL METHODS OF DETECTION

One analytical method of detection for azaconazole in effluents and sediments was supplied by Environment Canada (12). For effluents, a 500 ml sample is extracted with dichloromethane. The extract is filtered, concentrated, and the residue is then dissolved in n-hexane/methanol. The sample is analysed by gas chromatography/mass spectrometry (detection limits unspecified). For sediments, a 15 gram sample is extracted with methanol, filtered, diluted with water, then partitioned with dichloromethane. Minimum detectable concentrations for these analytical techniques were not provided.

In a volatilization study, gas-liquid chromatography was used for analysis of azaconazole in light petroleum solvent (white spirit) traps (11). The chromatograph was equipped with an electron-capture detector, and the concentrations of azaconazole were determined by external standardization. The detection limit was 5 ppb (11). Other analytical methodologies have been described in other references (33, 47, 48, 49, 50).

13.0 EXISTING LEGISLATION

Azaconazole was temporarily registered for use as an antisapstain compound by Agriculture Canada in 1990. Current antisapstain regulations in British Columbia (13) do not include criteria for azaconazole in effluents and air. Information on legislation in the United States could not be obtained from the Environmental Protection Agency.

14.0 CONCLUSION

Studies supplied by the manufacturer of azaconazole indicate that the chemical is stable to hydrolysis, but will undergo photodegradation, soil degradation, and degradation in the aquatic environment. Half-lives are on the order of several months. Azaconazole is well adsorbed in soils, and the chemical has a low leaching potential. Risk of groundwater contamination is therefore expected to be low.

Azaconazole is rapidly adsorbed, metabolised, and excreted by laboratory animals, and does not appear to bioaccumulate. However, a placental/milk transfer study is not available, so risk of fetal/neonatal exposure is uncertain. Such studies are recommended.

According to toxicity scales used in this report, technical grade azaconazole is moderately to very toxic to mammals, depending on species tested and route of exposure. The technical grade product is considered slightly toxic to several fish species; one formulation containing azaconazole (Rodewod 200 EC) is considered moderately toxic to two fish species tested.

Carcinogenicity, mutagenicity, and teratogenicity studies have all given negative results. Studies indicate a low risk for aerial exposure to azaconazole volatilized from wood treated with the compound. However, occupational exposure studies are not available. To adequately assess the safety of azaconazole use in wood protection, the dermal and inhalation risk associated with both occupational and incidental exposure should be investigated.

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Table 1: Comparison of toxicity data for various antisapstain chemicals.

	Oral LD50* Rat - mg/kg	Dermal LD50* Rabbit - mg/kg	Aquatic 96hrLC50* Fish species*-ppm
DDAC	84[15]	>1600[15]	0.44[15] Bluegills 0.27[15]
IPBC	1426[2]	>1940[2]	0.065[2]
TCMTB	360[16]	>324[16]	0.017[16] Chinook 0.015[16]
Copper-8	702[17]	>1960[17]	0.00016[17]
Azaconazole	262[43]	>1910[43]	20.8[45] Bluegills 14[44]
Rodewod 200 EC‡	166[41]	>360[46]	2.9[45] Chinook 2.3[45]
Sodium Carbonate	4,000[18]	not avail.	100[18]
Sodium Borate	2,660[18]	>2000[18]	377[18]
NaT$_4$CP	210[19]	270[19]	0.3-0.13[19]
NaPCP	71[20]	250[21]	0.048[22] Coho Salmon 0.032[24]
PCP	27[21]	39[20]	0.044[23] Bluegills 0.020[23]

*Values quoted are the lowest published for each species, and are based on 100% active ingredients, although less potent formulations may have been tested.

**Fish species is Rainbow trout unless otherwise noted.

‡Formulation toxicity values are included to illustrate increased toxicity of formulation over that of active ingredient.

APPENDIX A

Databases searched for information on azaconazole

The following computerized databases were searched for information on azaconazole:

CA Search
Toxline
Toxlit
AQUIRE
Medline
RTECS
CCOHS
IRIS

APPENDIX B

MAMMALIAN LETHAL TOXICITY CLASSES FOR CHEMICAL COMPOUNDS*

Toxicity Rating	Commonly Used Term	Oral/Dermal** (mg/kg)	Inhalation‡ (ppm -mg/L)
1	Practically Nontoxic	>15,000	>200
2	Slightly Toxic	5,000-15,000	20-200
3	Moderately Toxic	500-5,000	2-20
4	Very Toxic	50-500	0.2-2
5	Extremely Toxic	5-50	0.02-0.2
6	Ultra Toxic	<5	<0.02

*Toxicity ratings adapted from references 25, 26, and 27.

**Index: acute oral or dermal LD50.

‡Index: LC50 - four hour inhalation exposure.

APPENDIX C

AQUATIC LETHAL TOXICITY CLASSES FOR CHEMICAL COMPOUNDS*

Toxicity Rating	Commonly Used Term	Exposure Conc.** (ppm - mg/L)
1	Practically Nontoxic	>100
2	Slightly Toxic	10-100
3	Moderately Toxic	1-10
4	Very Toxic	0.1-1
5	Extremely Toxic	0.01-0.1
6	Ultra Toxic	<0.01

*Toxicity ratings adapted in consultation with reference 28.

**Index: 96 hour LC50 or EC50.